UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,166	11/17/2003	Ting-Dong Zhang	WAX017-185360C	4088

7590 08/09/2007

Eric A. Dichter, Esquire
Wolf, Block, Schorr and Solis-Cohen LLP
22nd Floor
1650 Arch Street
Philadelphia, PA 19103-2097

EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
08/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,166	ZHANG, TING-DONG	
	Examiner	Art Unit	
	JOHN PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/702,011.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 20070805
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 12 and 15-16 are pending in this application.

It is noted at the outset that applicant filed a translation of a certified copy of the foreign priority document with a statement that the translation is accurate during the prosecution of the parent application. For completeness of the record, applicant is advised to file those same documents in this application. This Office action will assume those documents will be filed herein in response to this Office action.

It is further noted that claims 12 and 15-16 were allowed in the previous Office action. After further consideration and review, the indication of allowability must be withdrawn. The Examiner now appreciates a different interpretation of the prior art vis-à-vis the claim language "comprising" in claim 12. The new ground of rejection set forth below will fully explain the Examiner's rationale.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. in view of Zhang et al., Shimotsuura et al., Remington's

Pharmaceutical Sciences (hereinafter Remington's), The Merck Index and Forkner et al.[1]

Zhang et al. (Zhang Peng et al.)[2] disclose that "713," which contains As_2O_3, is used to treat acute promyelocytic leukemia, APL (translation page 2, first paragraph). 10 ml of "713" in 300 ml of 5% glucose is disclosed (id.). One course of treatment was 28 days (id.) and one to three courses of treatment averaged 51.1 days for patients with CR, complete remission, outcome (translation page 2, section 1.1). "713" is disclosed to possess "relatively high therapeutic effect on APL, the side effects are few and light" (translation page 4, lines 14-15). Mechanism of action of "713" is induction of promyelocytes to continuously differentiate and programmed death for granular system (paragraph bridging translation pages 4-5).

Zhang et al. (Zhang Tingdong et al.)[3] disclose Ai-Ling I for treatment of acute granulocytic leukemia (translation page 2). 27.2% cure rate is reported (id.). Ai-Ling I is disclosed to contain 1 mg As_2O_3 and 0.01 mg $HgCl_2$ in 1 ml volume, with each dosage being 20 ml (translation page 3, lines 9-11). This calculates to **0.1 w/v% As_2O_3 and 0.001 w/v% $HgCl_2$**. The intravenous injection frequency is twice a day and treatment duration is 1-2 months (translation page 3, lines 10-15). Different Chinese medicines

[1] All references were cited by applicant in the PTO-1449 of 11/2003.
[2] Cited by applicant, see the PTO-1449 of 11/2003, page 3, 6th document.
[3] Cited by applicant, see the PTO-1449 of 11/2003, page 3, 7th document.

are administered as separate treatments, according to clinical symptoms, such as for "blood cooling" and "moist heat removal" (translation page 3, line 16 to page 4, line 6).

Shimotsuura et al. disclose that antineoplasmic actions of As_2O_3 are primarily achieved by DNA composition blockage (translation page 25, second full paragraph). Compared to a known antineoplastic agent, 5-FU, various activity was observed in many animal in vivo experiments, including 23.5% increase in life span for 5 mg As_2O_3 per kg oral adm. versus 32.8% increase in life span for 10 mg 5-FU per kg oral adm. (see Tables 1-2).

Remington's is cited to establish the well-known pharmaceutical formulation fact that glucose + sodium chloride is a commonly used IV fluid mixture and sterility of substances is an important element in IV protocol (see pages 1570-1580, in particular pages 1571, 1572 left column, 1576 right column). 5-20% dextrose (glucose) mixed with 0.22-0.9% sodium chloride is disclosed (seepage 1571, Table I, entry for "Dextrose and Sodium Chloride").

The Merck Index is cited to establish the well-known fact that As_2O_3 in admixture with potassium bicarbonate, alcohol and water (known as Fowler's solution) is a recognized antineoplastic agent (page 1098, #7479). The article by Forkner et al. is cited to establish that arsenic has long been known to be useful in treating leukemia (see pages 3-5). The form of arsenic is Fowler's solution (pages 3-5).

The primary reference by Zhang et al. does not explicitly disclose all the features required in the instant claims.

0.1-1 wt% As_2O_3

Zhang et al. disclose 10 ml of "713" (which contains As_2O_3) in 300 ml of 5% glucose (translation page 2, first paragraph). How much As_2O_3 is in the "713" is not expressly disclosed. However, the secondary reference by Zhang et al. teaches that 0.1 w/v% As_2O_3 is effective for treating acute granulocytic leukemia. Additionally, all of the cited references teach that arsenic has long been known to have antineoplasmic activity, and Shimotsuura et al. teach that the activity is due to DNA composition blockage.

Taken with the 0.1 w/v% As_2O_3 specifically taught for acute granulocytic leukemia treatment, one having ordinary skill in the art would have been motivated to adjust the concentration of the well known antineoplasmic As_2O_3 within 0.1-1 wt% to obtain and expect maximum treatment with acceptable toxicity.

Even if it could be argued that such motivation would not have been found (the Examiner maintains that the motivation would have been found), one having ordinary skill in the art would have found it obvious to try 0.1-1 wt% As_2O_3. It is without question that treating cancer, leukemia in particular, with arsenic trioxide, a potential poison, is a recognized problem with potential toxicity issues. In the absence of a specific concentration dosage disclosure by the primary reference, one having ordinary skill in

the art would have turned to other prior art solutions, i.e. other As_2O_3 concentrations used in the prior art to treat cancer. Given the known toxicity of too much As_2O_3, the secondary reference Zhang's use of 0.1 w/v% As_2O_3 represented a finite number and a reasonable range around which predictable potential solutions would have been obtained. Since the primary reference explicitly teaches that As_2O_3-containing "713" provides complete remission, continuous differentiation, and programmed cell death, one having ordinary skill in the art would have had good reason to pursue the known non-toxic but therapeutic concentration range options within his or her technical grasp. In turn, because 0.1-1 wt% has the properties predicted by the prior art, it would have been obvious to formulate the leukemia treating composition with such concentration of As_2O_3.

0.8 wt% NaCl + 10 wt% glucose

As for the injection formulation of 0.8% NaCl and 10 wt% glucose, it has already been shown that As_2O_3 has been formulated with 5% glucose to treat leukemia. Further, Remington's establishes that 5-20% glucose mixed with 0.22-0.9% sodium chloride for injections and drug vehicles is standard enough to appear in a pharmaceutical handbook. Therefore, one having ordinary skill in the art would have been motivated to formulate 0.1-1 wt% As_2O_3 with a mixture of 0.8% NaCl + 1 wt% glucose with the expectation that the mixture would provide suitable injection or drug vehicle functionality.

IV Drip

Although the primary reference by Zhang et al. does not expressly disclose intravenous drip to a human for treating leukemia, one having ordinary skill in the art would have been taught from the secondary reference by Zhang et al. that intravenous injection of As_2O_3 for treating leukemia would be similarly applicable. Intravenous drip is suggested from one of only several intravenous options that are available to the ordinary skilled artisan. Therefore, one having ordinary skill in the art would have been motivated to administer as an intravenous drip, particularly in view of being able to more slowly administer the potentially side-effect inducing As_2O_3.

Administering on a daily basis for approximately 2-4 weeks

The primary reference by Zhang et al. disclose that one course of treatment was 28 days. One to three courses are taught. The secondary reference by Zhang et al. discloses twice daily treatment for 1-2 months.

Such treatment protocols using As_2O_3 would have at least suggested to the ordinary skilled artisan that 4 weeks of treatment on a daily basis would have been obvious. Repeating on a daily basis does not preclude repeating twice on a daily basis. Nonetheless, repeating once on a daily basis for 4 weeks is also suggested. One having ordinary skill in the art would have been motivated to adjust the concentration strength, dosage, and dosage frequency by monitoring patient response and progress.

In view of the prior art treatment schedules, administering daily for 4 weeks would have been fairly suggested.

Ceasing administration

The prior art teaching of finite number of treatment course(s) is a teaching of ceasing administration.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

It is noted that the parent application, now issued as U.S. Patent 6,720,011, uses the closed language "consisting of" with respect to the aqueous solution of As_2O_3 (see patent claims 1 and 3). The situation here is substantially different because the claims here use the open language "comprising." By using this open language, the present claims do not exclude prior art "713" that contains $HgCl_2$. It is for this reason that the Examiner now recognizes the error in indicating allowability of claims 12 and 15-16 in the previous Office action. The "comprising" language brings into the prior art that is reasonably available against the present claims prior art that was not applicable to the patented parent application claims.

For these reasons, all claims must be rejected.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

John Pak
Primary Examiner
Technology Center 1600